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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/283,431	04/01/1999	WEN-QIANG ZHOU	475.08.423	9988

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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/26/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/283,431	ZHOU ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 9, 2003 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4-6 are maintained as rejected under 35 U.S.C. 103(a) as being unpatentable over Metelev et al. (US patent No. 6,143,881) in combination with Ghosh et al. (reference B1 on PTO form 1449, filed April 24, 2000).

Claims 4-6 are drawn to oligonucleotides that consist of a region of deoxyribonucleotides that comprises alternating phosphodiester and phosphorothioate internucleoside linkages and one or more regions of 2'-O-substituted ribonucleotides, and further wherein the oligonucleotides comprise between 12 and 50 and 17 and 35 nucleotides. The specification discloses alternating to encompass any regular or irregular pattern of phosphodiester and phosphorothioate internucleoside linkages.

Metelev et al. teach hybrid oligonucleotides that comprise a region of 2'-O-substituted ribonucleotides at the termini of a region of deoxyribonucleotides. Metelev et al. teach their oligonucleotides wherein the nucleotides are linked by a mixture of phosphorothioate and phosphodiester linkages. The oligonucleotides taught by Metelev et al. comprise between 12 and 50 and 17 and 35 nucleotides. Metelev et al. do not explicitly teach an embodiment wherein the mixture of phosphorothioate and phosphodiester linkages occurs within the deoxyribonucleotide region of the oligonucleotide.

Ghosh et al. teach phosphorothioate-phosphodiester oligonucleotide co-polymers, including oligonucleotides that have alternating phosphorothioate and phosphodiester linkages with the same pattern as the preferred embodiments disclosed in the instant application. The oligonucleotides taught by Ghosh et al. comprise between 12 and 50 and 17 and 35 nucleotides. Ghosh et al. do not teach a region of 2'-O-substituted ribonucleotides in their phosphorothioate-phosphodiester oligonucleotide co-polymers.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Metelev et al. and Ghosh et al. to make a hybrid oligonucleotide comprising a region of alternating phosphorothioate and phosphodiester linkages, as taught by Ghosh et al., with a region of 2'-O-substituted ribonucleotides, as taught by Metelev et al. because Metelev et al. teach that hybrid oligonucleotides comprising phosphorothioate and phosphodiester linkages and 2'-O-substitued ribonucleotides and deoxyribonucleotides regions have superior properties of duplex formation, Rnase H activation and nuclease resistance which used as an antisense molecule. Ghosh et al. identify phosphorothioate-phosphodiester oligonucleotide co-polymers as the best design for an antisense molecule as it results in the advantages of reduced nuclease stability, specificity and hybridization (see for example, page 31). One of ordinary skill in the art would have been motivated to combine the phosphorothioate-phosphodiester oligonucleotide co-polymer design taught by Ghosh et al. into the hybrid oligonucleotide taught by Metelev et al. to obtain the benefits of antisense design taught by each Ghosh et al. and Metelev et al.

Therefore, the invention of claims 4-6, as a whole, would have been obvious to one of ordinary skill in the art at the time the instant invention was made.

Response to Arguments

In response to the rejection of record of claims 4-6 under 35 USC 103(a), as being unpatentable over Metelev et al. in combination with Ghosh et al., set forth in the prior Office action, mailed May 9, 2003, Applicant argues that there is no motivation to combine the cited references. This argument has been fully considered, but not found to be persuasive.

Applicant argues that Ghosh et al. teach several desirable properties for phosphodiester oligonucleotides incorporating phosphorothioate bonds, however, Ghosh et al. also teach that all-phosphorothioate oligonucleotides have a reduced melting temperature relative to all-phosphodiester oligonucleotides and that co-polymers have intermediate melting temperatures. Applicant argues that Metelev et al. teaches that their 2'-OMe modifications solve the problem of reduced hybridization observed with all-phosphorothioate oligonucleotides by enhancing duplex formation. Applicant argues that Ghosh et al. teach that other antisense properties, like nuclease stability, are reduced in co-polymers and, therefore, the skilled artisan would be concerned that the introduction of phosphorothioates into the all phosphorothioate 2'-OMe oligos of Metelev et al. would negate the benefits observed by Metelev et al. by increasing nuclease susceptibility.

These arguments are not found to be persuasive because Ghosh et al. teach multiple benefits for incorporating co-polymers into an antisense, in addition to improved hybridization compared to all phosphorothioate oligos, including decreased non-specific protein binding and decreased non-specific translation inhibition at higher concentration. Ghosh et al. also indicate that although there is greater nuclease susceptibility in some co-polymers, particular backbone designs are more nuclease resistant than others and some are even comparable to all-phosphorothioate oligonucleotides. Ghosh et al. indicate that co-polymers have the best mixture of properties for use in antisense. Further, Metelev et al. indicate that the 2'-OMe modifications enhance nuclease stability as well as duplex formation, and, therefore, would enhance one of the shortcomings Applicant argues to be present in the oligos taught by Ghosh et al. The properties

of the Ghosh et al. oligos and the Metelev et al. oligos dovetail and, therefore, would be obvious to combine for the skilled artisan.

Conclusion

Any rejection of record not repeated herein is considered to be withdrawn.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
August 25, 2003

KAREN LACOURCIERE
PATENT EXAMINER